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Claims

1. An isolated nucleic acid molecule, comprising:

(a) nucleic acid molecules which hybridize under stringent conditions to a molecule consisting of a nucleic acid of SEQ ID NO:1 and which code for a cbl-SL polypeptide,

(b) deletions, additions and substitutions of (a) which code for a respective cbl-SL polypeptide,

(c) nucleic acid molecules that differ from the nucleic acid molecules of (a) or (b) in codon sequence due to the degeneracy of the genetic code, or

(d) complements of (a), (b) or (c).

2. The isolated nucleic acid molecule of claim 1, wherein the isolated nucleic acid molecule comprises SEQ ID NO:1.

3. The isolated nucleic acid molecule of claim 1, wherein the isolated nucleic acid molecule is the nucleic acid molecule of SEQ ID NO:3 or a fragment thereof.

4. An isolated nucleic acid molecule selected from the group consisting of

(a) a unique fragment of nucleic acid molecule of SEQ ID NO:1,

(b) complements of (a),

provided that the unique fragment includes a sequence of contiguous nucleotides which is not identical to any sequence selected from the sequence group consisting of

(1) sequences having the database accession numbers of Table I,

(2) complements of (1), and

(3) fragments of (1) and (2).

5. The isolated nucleic acid molecule of claim 4, wherein the sequence of contiguous nucleotides is selected from the group consisting of:

(1) at least two contiguous nucleotides nonidentical to the sequence group,

(2) at least three contiguous nucleotides nonidentical to the sequence group,

(3) at least four contiguous nucleotides nonidentical to the sequence group,

(4) at least five contiguous nucleotides nonidentical to the sequence group,

(5) at least six contiguous nucleotides nonidentical to the sequence group,

(6) at least seven contiguous nucleotides nonidentical to the sequence group.

6. The isolated nucleic acid molecule of claim 4, wherein the fragment has a size selected from the group consisting of at least: 8 nucleotides, 10 nucleotides, 12 nucleotides, 14 nucleotides, 16 nucleotides, 18 nucleotides, 20, nucleotides, 22 nucleotides, 24 nucleotides, 26 nucleotides, 28 nucleotides, 30 nucleotides, 50 nucleotides, 75 nucleotides, 100 nucleotides, and 200 nucleotides.

7. The isolated nucleic acid molecule of claim 4, wherein the molecule encodes a polypeptide which is immunogenic.

8. An expression vector comprising the isolated nucleic acid molecule of claims 1, 2, 3, 4, 5, 6, or 7 operably linked to a promoter.

9. An expression vector comprising the isolated nucleic acid molecule of claim 4 operably linked to a promoter.

10. A host cell transformed or transfected with the expression vector of claim 8.

11. A host cell transformed or transfected with the expression vector of claim 9.

12. An isolated polypeptide encoded by the isolated nucleic acid molecule of claim 1, 2, 3, or 4, wherein the polypeptide, or fragment of the polypeptide, has cbl-SL activity.

13. The isolated polypeptide of claim 12, wherein the isolated polypeptide is encoded by the isolated nucleic acid molecule of claim 2.

14. The isolated polypeptide of claim 13, wherein the isolated polypeptide comprises a polypeptide having the sequence of amino acids 1-474 of SEQ ID NO:2.

15. An isolated polypeptide encoded by the isolated nucleic acid molecule of claim 1, 2, or 3, wherein the polypeptide, or fragment of the polypeptide, is immunogenic.

16. The fragment of claim 15, wherein the fragment, or portion of the fragment, binds to a human antibody.

17. An isolated binding polypeptide which binds selectively a polypeptide encoded by the isolated nucleic acid molecule of claim 1, 2, 3, or 4.

18. The isolated binding polypeptide of claim 17, wherein the isolated binding polypeptide binds to a polypeptide having the sequence of amino acids of SEQ ID NO:2 or SEQ ID NO:10.

19. The isolated binding polypeptide of claim 17, wherein the isolated binding polypeptide binds to a polypeptide having the sequence of amino acids of SEQ ID NO:2.

20. The isolated binding polypeptide of claim 19, wherein the isolated binding polypeptide is an antibody or an antibody fragment selected from the group consisting of a Fab fragment, a $F(ab)_2$ fragment or a fragment including a CDR3 region selective for the polypeptide having the sequence of amino acids of SEQ ID NO:2.

21. An isolated polypeptide comprising a fragment of the polypeptide of claim 12 of sufficient length to represent a sequence unique within the human genome and identifying a polypeptide that has cbl-SL activity, provided that the fragment excludes a sequence of contiguous amino acids encoded by an isolated nucleic acid selected from the group consisting of SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8, and SEQ ID NO:9.

22. A kit, comprising a package containing:

an agent that selectively binds to the isolated nucleic acid of claim 1 or an expression product thereof, and

a control for comparing to a measured value of binding of said agent to said isolated nucleic acid of claim 1 or expression product thereof.

23. The kit of claim 22, wherein the control is a predetermined value for comparing to the measured value.

24. The kit of claim 23, wherein the control comprises an epitope of the expression product of the nucleic acid of claim 1.

25. A method for determining the level of cbl-SL expression in a subject, comprising:

a) obtaining a test sample from a subject,

b) measuring the expression of cbl-SL in the test sample,

c) comparing the measured expression of cbl-SL to a control.

26. The method of claim 25, wherein the expression of cbl-SL in (b) is cbl-SL mRNA expression.

27. The method of claim 25, wherein the expression of cbl-SL in (b) is cbl-SL polypeptide expression.

28. The method of claim 25, wherein the test sample is tissue.

29. The method of claim 25, wherein the test sample is a biological fluid.

30. The method of claim 26, wherein cbl-SL mRNA expression is measured using the Polymerase Chain Reaction (PCR).

31. The method of claim 26, wherein cbl-SL mRNA expression is measured using northern blotting.

32. The method of claim 27, wherein cbl-SL polypeptide expression is measured using monoclonal antisera to cbl-SL.

33. The method of claim 27, wherein cbl-SL polypeptide expression is characterized using polyclonal antisera to cbl-SL.

34. A method of screening for the presence of a carcinoma in a subject suspected of having a carcinoma, comprising:

(a) characterizing cbl-SL nucleic acid sequences in a test sample, wherein the test sample is obtained from the subject;

(b) comparing the cbl-SL nucleic acid sequences of the test sample to cbl-SL nucleic acid sequences of a control sample,

wherein an observed alteration or match in a cbl-SL nucleic acid sequence in the tissue sample as compared to the cbl-SL nucleic acid sequences in the control sample, is indicative of the presence of carcinoma in the subject.

35. The method of claim 34, wherein the observed alteration is apparent when a cbl-SL nucleic acid sequence in the tissue sample is compared to wild-type cbl-SL nucleic acid sequences in the control sample.

36. The method of claim 34, wherein the observed match is apparent when a cbl-SL nucleic acid sequence in the tissue sample is compared to mutant cbl-SL nucleic acid sequences in the control sample.

37. The method of claim 34, wherein cbl-SL mRNA molecules are compared.

38. The method of claim 37, wherein alteration of cbl-SL mRNA is detected by hybridization of mRNA from said tissue sample to a cbl-SL nucleic acid of claim 1, 2, or 3.

39. The method of claim 38, wherein cbl-SL cDNA sequences are compared, said comparing performed by hybridization of a cbl-SL cDNA probe to genomic DNA isolated from said tissue sample.

40. The method of claim 39, further comprising:

(a) subjecting genomic DNA isolated from a non-neoplastic tissue of the subject to Southern hybridization with the cbl-SL cDNA probe; and

(b) comparing the hybridizations of:

(i) the cbl-SL cDNA probe to said tissue sample and (ii) the cbl-SL cDNA probe to said non-neoplastic tissues.

41. The method of claim 39, wherein the cbl-SL cDNA probe detects a restriction fragment length polymorphism.

42. The method of claim 34, wherein cbl-SL nucleic acid sequences are compared, said comparing being performed by determining the sequence of all or part of a cbl-SL cDNA in said tissue sample using a polymerase chain reaction,

wherein deviations in the Cbl-SL cDNA determined from that of the wild-type Cbl-SL nucleic acid sequence shown in SEQ ID NO: 1, is indicative of the presence of the carcinoma in the subject.

43. The method of claim 34, wherein the alteration of cbl-SL nucleic acid sequences is detected by identifying a mismatch between molecules (a) a cbl-SL cDNA or cbl-SL mRNA isolated from said tissue and (b) a nucleic acid probe complementary to the human wild-type

cbl-SL nucleic acid sequence, when molecules (a) and (b) are hybridized to each other to form a duplex.

44. The method of claim 34, wherein cbl-SL nucleic acid sequences are compared and the alteration of cbl-SL nucleic acid sequences is detected by the steps of:

(a) amplifying Cbl-SL cDNA sequences in said tissue sample, and

(b) hybridizing the amplified cbl-SL cDNA sequences to nucleic acid probes which comprise Cbl-SL sequences.

45. The method of claim 34, wherein cbl-SL nucleic acid sequences are compared and the alteration of Cbl-SL nucleic acid sequences is detected by molecular cloning of Cbl-SL genes in said tissue sample and sequencing all or part of the cloned Cbl-SL gene.

46. The method of claim 34, wherein the detection of alteration of Cbl-SL nucleic acid sequences comprises screening for a deletion mutation.

47. The method of claim 34, wherein the detection of alteration of Cbl-SL nucleic acid sequences comprises screening for a point mutation.

48. The method of claim 34, wherein the detection of alteration of Cbl-SL nucleic acid sequences comprises screening for an insertion mutation.

49. The method of claim 34, wherein said tissue is selected from the group consisting of brain, heart, serum, breast, colon, bladder, uterus, prostate, stomach, testis, ovary, pancreas, pituitary gland, adrenal gland, thyroid gland, salivary gland, mammary gland, kidney, liver, intestine, spleen, thymus, bone marrow, trachea, and lung.

50. A pharmaceutical composition comprising:

a pharmaceutically effective amount of an agent comprising of an isolated nucleic acid molecule of claim 1 or an expression product thereof, and

a pharmaceutically acceptable carrier.

51. The pharmaceutical composition of claim 50, wherein the agent is an expression product of the isolated nucleic acid molecule of claim 1.

52. A method for determining the level of cbl-SL expression in a subject, comprising:

a) measuring the expression of cbl-SL in a test sample, wherein the test sample is obtained from the subject; and

b) comparing the measured expression of cbl-SL to a control.

53. A method for increasing cbl-SL expression in a subject that expresses a mutant cbl-SL, comprising:

administering an isolated cbl-SL nucleic acid molecule of the invention or an expression product thereof to a subject expressing a mutant cbl-SL, in an amount effective to increase wild-type cbl-SL expression in the subject.

54. A method for downregulating expression of a tyrosine kinase in a cell, comprising:

contacting a cell expressing a tyrosine kinase with a cbl-SL polypeptide, in an amount effective to downregulate expression of the tyrosine kinase in the cell.

55. The method of claim 54, wherein the tyrosine kinase is selected from the group consisting of a receptor tyrosine kinase and a non- receptor tyrosine kinase.

56. The method of claim 54, wherein the receptor tyrosine kinase is EGFR.

57. The method of claim 54, wherein the cbl-SL polypeptide is a polypeptide having an amino acid sequence consisting of the sequence set forth in SEQ ID NO:2.

58. The method of claim 54, wherein the cbl-SL polypeptide is encoded by the nucleic acid of SEQ ID NO:1.

59. The method of claim 54, wherein the tyrosine kinase is ligand activated.

60. The method according to anyone of claims 54-58, wherein the tyrosine kinase is phosphorylated.

61. A method for identifying lead compounds for an agent that regulates cbl-SL activity, comprising:

(a) forming a mixture of a cbl-SL polypeptide, a tyrosine kinase that binds a cbl-SL polypeptide, and a candidate agent,

(b) incubating the mixture under conditions which permit specific binding of the tyrosine kinase that binds a cbl-SL polypeptide to the cbl-SL polypeptide,

(c) detecting a reference specific binding of the tyrosine kinase that binds a cbl-SL polypeptide to the cbl-SL polypeptide, the reference specific binding being indicative of cbl-SL activity, and

(d) comparing the reference specific binding to a control.

62. The method of claim 61, wherein the tyrosine kinase is selected from the group consisting of a receptor tyrosine kinase, a non- receptor tyrosine kinase, and any of the foregoing tyrosine kinases in complex with another agent.

63. The method of claim 61, wherein the receptor tyrosine kinase is EGFR.

64. The method of claim 61, wherein the cbl-SL polypeptide is a polypeptide having an amino acid sequence consisting of the sequence set forth in SEQ ID NO:2.

65. The method of claim 61, wherein the cbl-SL polypeptide is encoded by the nucleic acid of SEQ ID NO:1.

66. The method of claim 61, wherein the tyrosine kinase is ligand activated.

67. The method according to anyone of claims 61-65, wherein the tyrosine kinase is phosphorylated.

68. The method of claim 61, further comprising adding an intermediate adapter into the mixture.

69. The method of claim 68, wherein the intermediate adapter is Grb2.